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TITLE: Clinical Comparative Bioavailability Study of ICN- and
Roche-Manufactured 30 mg Pyridostigmine Bromide Tablets in
Healthy Volunteers

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13. Abstract (Maximum 200 Words) (abstract should contain no proprietary or confidential information)

Pyridostigmine Bromide 30 mg tablets manufatcured by ICN Canada and Roche UK were studied in a two treatment, crossoverdesign bioavailability study. Plasma samples obtained from the 30 healthy subjcets that completed the study were analyzed using a validated LC/MS/MS method and concenrations were used to determine bioequivalence. The products were found to be bioequivalen based upon the 90% confidence intervals of the logarithmically transformed AUC 0-T, AUC 0-Infinity and CMAX. The confidence intervals surrounding the ratios of test versus reference means were within th 0.80 to 1.25 bioequivalence limits.

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SUMMARY OF STUDY RESULTS

1.0   Title

Clinical Comparative Bioavailability Study of ICN- and Roche-Manufactured 30 mg Pyridostigmine Bromide Tablets in Healthy Volunteers

2.0   Objective

The objective of this study was to compare the relative bioavailability of pyridostigmine bromide 30 mg tablets manufactured by Roche UK with that of pyridostigmine bromide 30 mg tablets, manufactured by ICN Canada.

3.0   Methods

The study was conducted at PharmaKinetics Laboratories, Inc., Baltimore, Maryland, and included the clinical conduct, analytical determination of plasma pyridostigmine concentrations, and statistical analysis. Thirty-two healthy male and female subjects were enrolled in this two-treatment crossover study. Blood samples from all subjects who completed the study were to be analyzed. The subjects were to receive a single 30 mg oral dose of pyridostigmine bromide on two occasions separated by a washout period of one week. Blood samples were obtained at 17 time points from predose (0 hour) until 12 hours post-dose. The Clinical Summary details the conduct of the entire study.

The plasma samples were analyzed by a specific, validated LC/MS/MS method to determine pyridostigmine concentrations. The concentrations were used to calculate the area under the concentration-time curve to the last non-zero time point (AUC 0-T), elimination rate constant (Kel), half-life (T½) and AUC 0-Infinity (AUC 0-Inf). The actual times of sample collections were used in the calculations. The maximum drug concentration (CMAX) and the time to maximum drug concentration (TMAX) were also reported. The arithmetic mean and standard deviation were calculated for each parameter and for the pyridostigmine concentrations at each time point. The geometric means were calculated for AUC 0-T, AUC 0-Infinity and CMAX. All parameters were analyzed by analysis of variance (ANOVA) and an F-test to determine statistically significant differences ($\alpha=0.05$). The analysis of variance included sequence, subject nested within sequence, period, and drug treatment in the statistical model. The power of the study to detect a 20% difference in parameter means as statistically significant at the 5% level of the t-distribution was calculated for each pharmacokinetic metric. The ratios of the test and reference means and geometric means were reported using least squares means from the ANOVAs. Bioequivalence was determined using the two one-tailed tests procedure, accomplished by constructing a 90% confidence interval

for each difference in treatment means, and then re-expressing it as a confidence interval for the ratio of the means (test/reference). The products were considered bioequivalent if the 90% confidence interval about the ratio of means (test/reference) for logarithmically transformed AUC and CMAX were contained within the limits 0.80 to 1.25.

4.0   Results

Of the 32 subjects enrolled into the study, 30 subjects completed. Two of the subjects withdrew prematurely from the study. Subject 18 withdrew prior to entry of period II because of flu-like symptoms, including fever, chills, bodyache and coughing, experienced from June 28 through July 03, 2001. Subject 3 failed to return to the facility to complete period II.

The plasma samples were analyzed for the 30 completed subjects. The concentration of pyridostigmine at each time point after each product is summarized in Table 1 of this summary. The mean concentration at 2.33 and 5 hours after administration of the ICN product were statistically significantly higher ($\alpha=0.05$) than the mean concentrations after administration of the Roche product. At all other times post-dose there were no statistically significant differences. The mean pyridostigmine concentration measured at each time point after administrations of the two products were plotted on a rectilinear scale (Figure 1) and on a semi-logarithmic scale (Figure 2).

The sampling schedule proved to be suitable for this bioavailability study. Eighty percent of AUC 0-Infinity was measured by AUC 0-T for 59 of the 60 estimates obtained. The first post-dose sample was not the maximum observed concentration after any of the doses. At least six post-dose samples were obtained before the average time of the maximum concentration.

The arithmetic means ± standard deviation for each parameter are presented in Table 2 and the results of the analysis of variance are presented in Table 3. The detailed analyses and tabulations are presented in the Drug Levels and Statistical Appendix I sections of this report.

There were statistically significant ($\alpha=0.05$) differences between the formulations for AUC 0-T, CMAX and LN CMAX. There was no statistically significant sequence effect ($\alpha=0.10$) or period effect ($\alpha=0.05$) for any of the pharmacokinetic parameters.

Based on the least squares means of the logarithmically transformed parameters, the AUC 0-T and AUC 0-Infinity for the ICN test product were 9% and 8% higher than the respective estimates for the Roche reference product. The CMAX for the test

product was 11% higher than that for the reference product and occurred 5% later (6 minutes). The 90% confidence intervals for the parameters were AUC 0-T [1.01; 1.18], AUC 0-Infifnity [1.00; 1.17] and CMAX [1.02; 1.20].

5.0 Conclusion

The pyridostigmine 30 mg tablet product manufactured by ICN Canada was observed to be bioequivalent to the 30 mg tablet product manufactured by Roche UK when both were administered under fasted conditions. The 90% confidence intervals surrounding the ratios of the test versus reference product means for AUC 0-T, AUC 0-Infinity and CMAX were within the 0.80 - 1.25 bioequivalence limits.

TABLE 1: PYRIDOSTIGMINE PLASMA CONCENTRATIONS (ng/mL)
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 30)
#205-01-11618

Time (h)	Test: ICN (Canada)			Ref: Roche (UK)			Ratio Test/Reference	Significance
	N	Mean	± Std. Dev.	N	Mean	± Std. Dev.		
0	30	0.0000		30	0.0000		--	--
0.33	30	2.453	± 1.973	30	1.870	± 1.491	1.31	N.S.
0.67	30	9.524	± 5.684	30	10.07	± 4.436	0.95	N.S.
1	30	12.62	± 6.182	30	11.86	± 5.816	1.06	N.S.
1.33	30	14.12	± 6.286	30	13.60	± 6.636	1.04	N.S.
1.67	30	15.79	± 7.425	30	14.14	± 6.134	1.12	N.S.
2	30	16.30	± 8.518	30	14.31	± 5.688	1.14	N.S.
2.33	30	15.27	± 6.827	30	13.39	± 5.012	1.14	p<0.05
2.67	30	14.84	± 6.746	30	13.38	± 4.788	1.11	N.S.
3	30	13.61	± 5.996	30	12.18	± 4.761	1.12	N.S.
3.5	30	12.79	± 5.882	30	11.33	± 5.216	1.13	N.S.
4	30	11.53	± 5.716	30	9.789	± 4.350	1.18	N.S.
5	30	9.593	± 4.697	30	8.255	± 3.763	1.16	p<0.05
6	30	6.982	± 3.413	30	6.012	± 2.700	1.16	N.S.
8	30	3.780	± 1.924	30	3.681	± 1.967	1.03	N.S.
10	30	2.419	± 1.396	30	2.245	± 1.303	1.08	N.S.
12	30	1.353	± 1.011	30	1.287	± 1.116	1.05	N.S.

*Based on Type III test from the analysis of variance (α=0.05).

TABLE 2: PHARMACOKINETIC PARAMETERS FOR PLASMA PYRIDOSTIGMINE
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 30)
#205-01-11618

Parameter	Test: ICN (Canada)			Ref: Roche (UK)			Test/ Reference
	N	Mean ± Std. Dev.	%CV	N	Mean ± Std. Dev.	%CV	
Ln AUC 0-T Geometric Mean[1]	30	4.3958 ± 0.4057 81.11		30	4.3066 ± 0.3585 74.19		1.09
Ln AUC 0-Inf Geometric Mean	30	4.4798 ± 0.3889 88.22		30	4.3993 ± 0.3512 81.39		1.08
Ln Cmax Geometric Mean	30	2.8878 ± 0.4356 17.95		30	2.7860 ± 0.3507 16.22		1.11
AUC 0-T (ng.h/mL)	30	87.88 ± 36.47	41.5	30	78.97 ± 29.24	37.0	1.11
AUC 0-Inf (ng.h/mL)	30	95.00 ± 38.03	40.0	30	86.51 ± 32.13	37.1	1.10
Cmax (ng/mL)	30	19.71 ± 8.897	45.1	30	17.24 ± 6.455	37.5	1.14
Tmax (h)	30	2.217 ± 1.014	45.8	30	2.111 ± 0.7170	34.0	1.05
Kel (1/h)	30	0.2677 ± 0.09552	35.7	30	0.2487 ± 0.05758	23.2	1.08
T1/2 (h)	30	2.804 ± 0.7254	25.9	30	2.920 ± 0.6429	22.0	0.96

[1] Antilogarithm of the mean of the log transformed parameter.

TABLE 3: PHARMACOKINETIC PARAMETERS FOR PLASMA PYRIDOSTIGMINE LEAST SQUARES MEANS ± STANDARD ERROR (N = 30)
#205-01-11618

Parameter	Test Test: ICN (Canada)	Reference Ref: Roche (UK)	Test/ Reference	Signif- icance	Study Power	Intrasubject C.V.(%)	90% Confidence Interval
Ln AUC 0-T Geometric Mean[1]	4.3958 ± 0.0322 81.11	4.3066 ± 0.0322 74.19	1.09	N.S.	0.99	17.8	1.01; 1.18
Ln AUC 0-Inf Geometric Mean	4.4798 ± 0.0316 88.22	4.3993 ± 0.0316 81.39	1.08	N.S.	0.99	17.4	1.00; 1.17
Ln Cmax Geometric Mean	2.8878 ± 0.0339 17.95	2.7860 ± 0.0339 16.22	1.11	p=0.0425	0.98	18.7	1.02; 1.20
AUC 0-T (ng.h/mL)	87.88 ± 2.951	78.97 ± 2.951	1.11	p=0.0416	0.95	19.4	1.02; 1.20
AUC 0-Inf (ng.h/mL)	95.00 ± 3.106	86.51 ± 3.106	1.10	N.S.	0.97	18.7	1.01; 1.18
Cmax (ng/mL)	19.71 ± 0.6933	17.24 ± 0.6933	1.14	p=0.0177	0.92	20.6	1.05; 1.24
Tmax (h)	2.217 ± 0.1072	2.111 ± 0.1072	1.05	N.S.	0.77	27.1	0.93; 1.17
Kel (1/h)	0.2677 ± 0.00769	0.2487 ± 0.00769	1.08	N.S.	0.99	16.3	1.00; 1.15
T1/2 (h)	2.804 ± 0.07065	2.920 ± 0.07065	0.96	N.S.	>0.99	13.5	0.90; 1.02

[1] Antilogarithm of the least squares mean of the log transformed parameter.
The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant (α=0.05), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

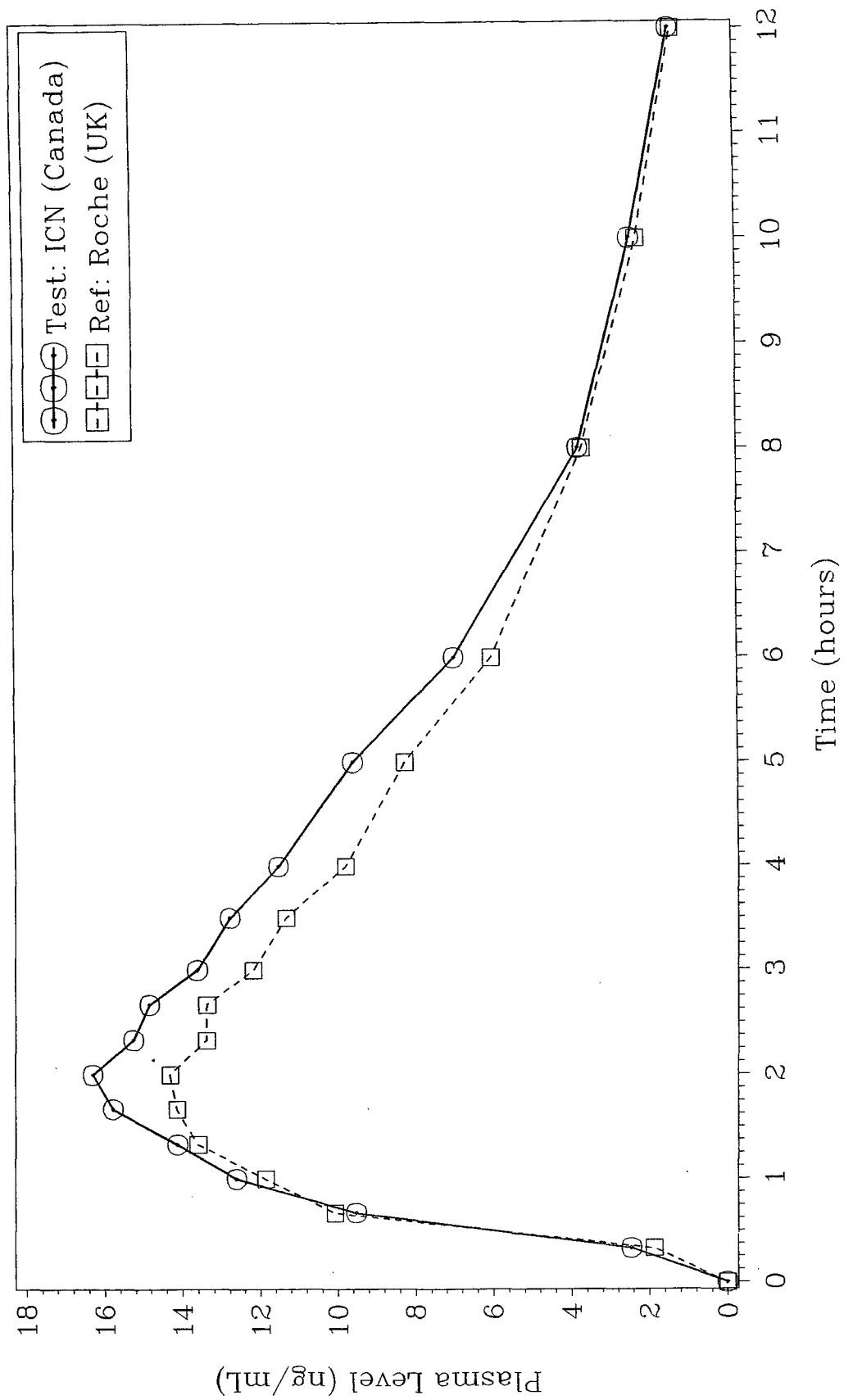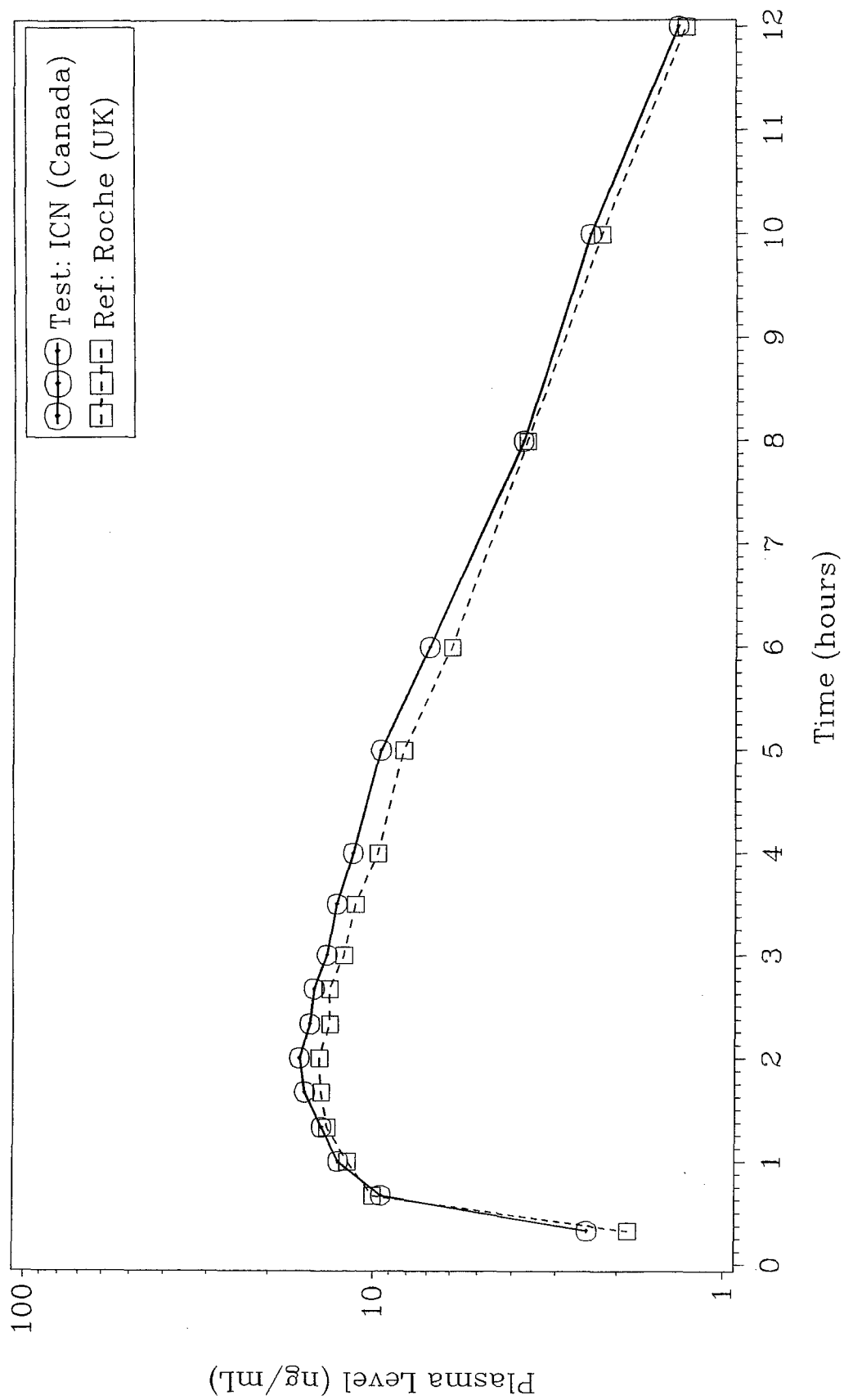Figure 1: Mean Pyridostigmine Plasma Levels
#205-01-11618
N = 30

Figure 2: Mean Pyridostigmine Plasma Levels (Semi−log Scale)
#205−01−11618
N = 30

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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